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THEMED ISSUE REVIEW

The role of platelet $P2Y_{12}$ receptors in inflammation

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Abstract

Inflammation is a complex pathophysiological process underlying many clinical conditions. Platelets contribute to the thrombo-inflammatory response. Platelet $P2Y_{12}$ receptors amplify platelet activation, potentiating platelet aggregation, degranulation and shape change. The contents of platelet alpha granules, in particular, act directly on leucocytes, including mediating platelet–leucocyte aggregation and activation via platelet P-selectin. Much evidence for the role of platelet $P2Y_{12}$ receptors in inflammation comes from studies using antagonists of these receptors, such as the thienopyridines clopidogrel and prasugrel, and the cyclopentyltriazolopyrimidine ticagrelor, in animal and human experimental models. These suggest that antagonism of $P2Y_{12}$ receptors decreases markers of inflammation with some evidence that this reduces incidence of adverse clinical sequelae during inflammatory conditions. Interpretation is complicated by pleiotropic effects such as those of the thienopyridines on circulating leucocyte numbers and of ticagrelor on adenosine reuptake. The available evidence suggests that $P2Y_{12}$ receptors are prominent mediators of inflammation and $P2Y_{12}$ receptor antagonism as a potentially powerful strategy in a broad range of inflammatory conditions.

KEYWORDS
inflammation, leucocytes, $P2Y_{12}$ receptors, platelets

1 | INTRODUCTION

Inflammation is a double-edged entity, important in the repair of tissue damage and fighting infection, but harmful when excessively or inappropriately stimulated. Inflammation is central to a broad range of diseases, including cardiovascular, infective, autoimmune, neoplastic, degenerative and metabolic conditions (Furman et al., 2019). For example, at the core of atherosclerotic cardiovascular disease (ASCVD) is inappropriate inflammation in response to endothelial injury and infiltration of the vessel wall by low-density and very-low-density lipoproteins, leading to plaque formation (Libby et al., 2019). In particular, transmigration of blood monocytes to become vessel wall macrophages that unsuccessfully attempt to clear lipid-rich debris is a key feature of atherogenesis. Furthermore, reducing inflammation in patients with ASCVD can reduce the risk of major adverse cardiovascular events (MACEs) (Ridker et al., 2017; Tardif et al., 2019). Likewise, though, in infections, inflammation can be an appropriate and useful host response, overstimulation of inflammation is responsible for severe consequences such as septic shock (Delano & Ward, 2016).

Platelets are small anucleate cells circulating in very high numbers, derived from megakaryocytes (Chang et al., 2007). Their primary physiological role is in haemostasis, but they can become inappropriately activated, for example, upon atherosclerotic plaque rupture or erosion, leading to thrombosis (Parker & Storey, 2018). Upon activation, platelets undergo shape change, aggregate and release further

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CCS, chronic coronary syndrome; CLP, caecal ligation and puncture; COVID-19, coronavirus disease 2019; GPIIb/IIIa, glycoprotein IIb/IIIa; MACEs, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCTs, randomised controlled trials; VASP, vasodilator-associated phosphoprotein.

prothrombotic mediators that propagate the thrombotic response. However, platelets also play a significant role in inflammation, including in settings such as atherogenesis, acute thrombosis or sepsis (Giustozzi et al., 2021).

The platelet **$P2Y_{12}$** receptor is key to the amplification of platelet activation response and is central in governing interactions between platelets and other inflammatory cells (Storey et al., 2000). In this review, we discuss the biology and pharmacology of the $P2Y_{12}$ receptor before focussing on its role in inflammation and how $P2Y_{12}$ receptor antagonists ('$P2Y_{12}$ inhibitors') can influence the inflammatory response. Though we focus on studies from the cardiovascular domain, this reflects the current clinical utility of $P2Y_{12}$ inhibitors. Other articles have considered this topic (Mansour et al., 2020; Thomas & Storey, 2015), but this fresh summary takes advantage of more recent findings from, for example, mechanistic studies of $P2Y_{12}$ inhibitors and clinical trial findings from the coronavirus disease 2019 (COVID-19) pandemic.

2 | PLATELET $P2Y_{12}$ RECEPTOR STRUCTURE AND FUNCTION

In humans, $P2Y_{12}$ receptors are encoded by the *P2RY12* gene (rs2046934), located on chromosome 3 (3q25.1), containing 47 kb with a product of 342 amino acids (Rudež et al., 2008). Molecular identification of $P2Y_{12}$ receptors was achieved in 2001 (Hollopeter et al., 2001). The greatest expression of these receptors occurs in platelets and areas of the brain (mostly midbrain) but has also been detected in vascular smooth muscle cells, lung and leucocytes (Gachet, 2012).

The endogenous ligand of the $P2Y_{12}$ receptor is **ADP** (Zhang et al., 2001). Although ADP is found in all cell types containing mitochondria and at low levels in the plasma, it is present at high concentrations in the dense granules in platelets and is released upon platelet activation (Storey, 2006).

The $P2Y_{12}$ receptor is a seven-transmembrane domain G protein-coupled receptor, linked to G_i, which is activated upon ADP binding, mediated by conformational change (Zhang et al., 2014). Though $P2Y_{12}$ does not play a major role in the initiation of platelet activation or aggregation, it plays a central role in the amplification of these processes (Storey et al., 2000). The α subunit of G_i mediates inhibition of the formation of **cAMP** by **adenylate cyclase**, reducing the activity of **PKA** (Knighton et al., 1991). In platelets, PKA is responsible for the phosphorylation of vasodilator-associated phosphoprotein (VASP) (Butt et al., 1994). Unphosphorylated VASP stimulates the externalisation of the **glycoprotein IIb/IIIa** (GPIIb/IIIa) complex, mediating the final common pathway of platelet aggregation (Horstrup et al., 1994). Activation of $P2Y_{12}$ receptors therefore increases the availability of unphosphorylated VASP, promoting platelet aggregation. The β–γ subunit of $P2Y_{12}$-coupled G_i further contributes to GPIIb/IIIa activation by stimulating **PI3K** activity, in turn increasing activity of **PKB (Akt)** (Cosemans et al., 2006). Importantly, PI3K also mediates platelet degranulation (Borst et al., 2012). This occurs via a number of downstream pathways, shown in Figure 1, leading to changes in actin dynamics, in turn resulting in migration and fusion of granules with the cell surface membrane and ejection of their contents (Aloui et al., 2014; Stegner & Nieswandt, 2011).

3 | ROLE OF $P2Y_{12}$-MEDIATED PLATELET ACTIVATION IN INFLAMMATION

Platelet granules released upon activation include those of the α and dense types, as well as lysosomes (Heijnen & van der Sluijs, 2015). Each of these types contributes to the proinflammatory effects of $P2Y_{12}$ receptor activation. The alpha granules contain high levels of **platelet P-selectin (CD62P)**, which is externally expressed upon fusion of the granule with the cell surface membrane (Harrison & Cramer, 1993). P-selectin binds to **P-selectin glycoprotein ligand-1 (PSGL-1)** on leucocytes, leading to formation of platelet–leucocyte aggregates. Specific actions depend on the leucocyte type. Platelet P-selectin interacting with monocyte PSGL-1, for example, promotes release of proinflammatory cytokines such as **TNF-α**, **IL-1β**, **IL-8** and the chemokine **CCL2**, via activation of the transcription factor NFκB pathway (Weyrich et al., 1995), additionally promoting surface expression of adhesion molecules (Martins et al., 2006). These cytokines induce the liver to release higher levels of C-reactive protein (CRP) (Yeh, 2004). Platelet–neutrophil aggregation promotes release of neutrophil extracellular traps (NETosis), which physically interact with pathogens and also contribute to many pathological inflammatory conditions, including atherosclerosis, thrombosis and sepsis (Etulain et al., 2015; Mozzini et al., 2017; O'Brien et al., 2017). Externalisation of GPIIb/IIIa induced by platelet activation also contributes to platelet–leucocyte aggregation through binding to the integrin **CD11b**, via bridging with **fibrinogen** (Schwarz et al., 2002).

As well as platelet P-selectin, the alpha granules contain a variety of soluble proinflammatory factors, released into the plasma upon fusion with the cell surface membrane. The range and effects of these are summarised in Table 1. These may directly modulate the activity of inflammatory cells or stimulate acellular coagulation. Stimulating the coagulation cascade results in an increase in the generation of factors such as **thrombin** or **activated protein C** that can activate specific cell receptors on mononuclear or endothelial cells and may affect, for example, cytokine production or inflammatory cell apoptosis (Levi et al., 2004). $P2Y_{12}$ receptor-mediated platelet activation also contributes further to thrombin generation via increasing scramblase activity leading to externalisation of **phosphatidylserine** on the platelet cell membrane, stabilising the prothrombinase complex (Bevers et al., 1982).

Dense granules contain high concentrations of ADP, **ATP** and **5-HT** (McNicol & Israels, 1999). Release of dense granules into the extracellular space leads to autocrine and paracrine positive feedback on platelet activation. As well acting on $P2Y_{12}$ receptors, ADP stimulates platelet **$P2Y_1$** receptors, which in contrast to $P2Y_{12}$ receptors play a significant role in the initiation of platelet activation, including shape change (Hechler et al., 1998). Stimulation of $P2Y_1$, but not $P2Y_{12}$ receptors, however, does not lead to sustained platelet activation. As well as effects on platelets, extracellular ADP contributes to inflammation through mechanisms such as activation of other members of the **P2Y receptor family** found on leucocytes and

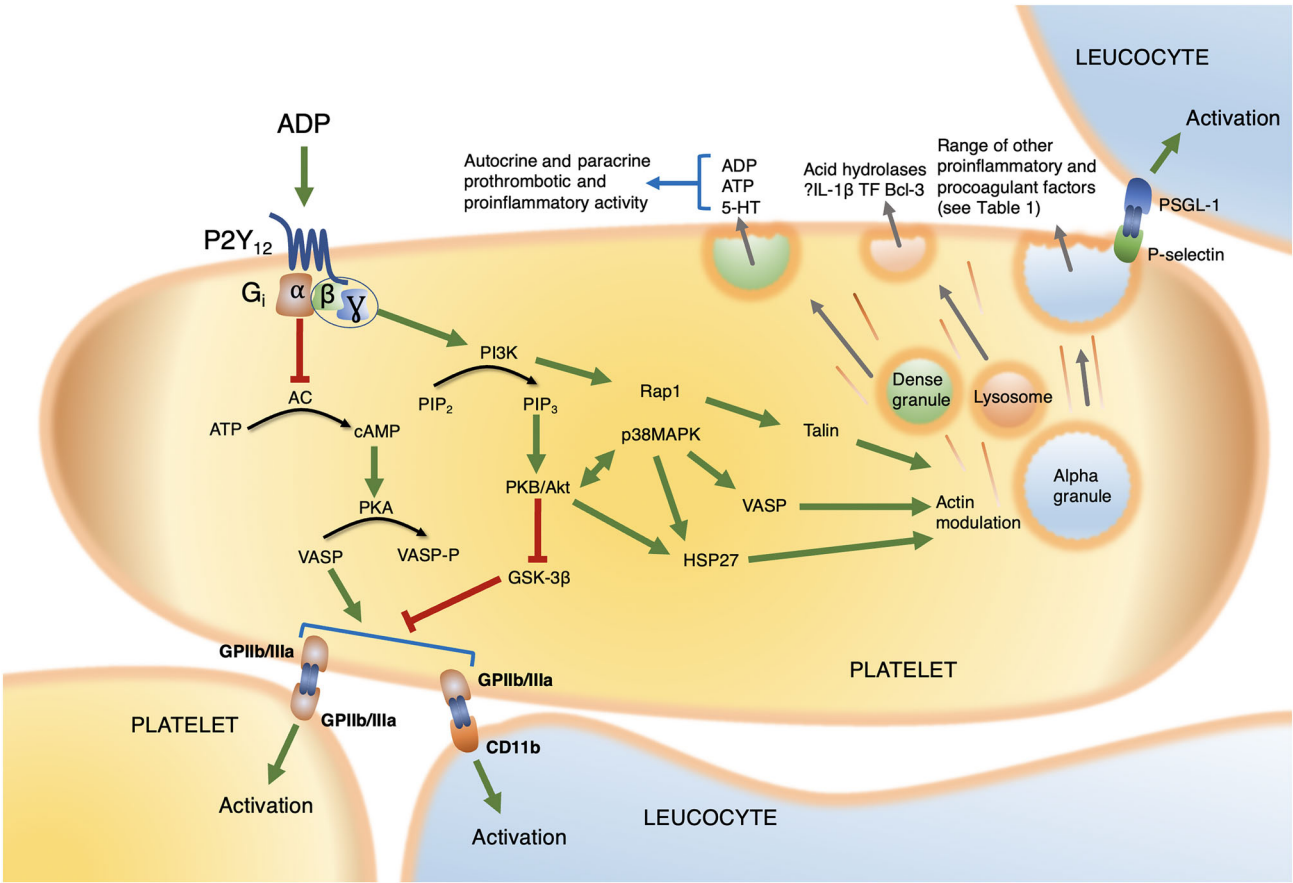

FIGURE 1 Signalling pathways upon platelet $P2Y_{12}$ receptor activation, potentiating platelet–platelet and platelet–leucocyte interaction. AC, adenylate cyclase; CD11b, cluster of differentiation 11b; GPIIb/IIIa, glycoprotein IIb/IIIa; GSK-3β, glycogen synthase kinase-3β; HSP27, heat shock protein 27; MAPK, mitogen-activated protein kinase; PIP, phosphatidylinositol bisphosphate; PKA, protein kinase A; PKB, protein kinase B; PSGL-1, P-selectin glycoprotein ligand 1; TF, tissue factor; VASP, vasodilator-associated phosphoprotein; VASP-P, phosphorylated vasodilator-associated phosphoprotein.

endothelium, and promotion of fibroblast proliferation (Borges et al., 2021). ATP is also an agonist at platelet **$P2X_1$** receptors, contributing to increased cytosolic calcium and resultant shape change and aggregation response, particularly in the presence of high shear stress (Mahaut-Smith et al., 2011). Extracellular ATP can also drive inflammasomal activation in monocytes (Cauwels et al., 2014). 5-HT contributes to platelet activation via the G_q-coupled **5-HT_{2A}** receptor and to a wide range of other inflammatory processes in other cell types (Wu et al., 2019).

Platelet lysosomes contain high concentrations of acid hydrolases, able to break down glycoproteins, glycolipids and glycosaminoglycans (Ciferri et al., 2000). Their role, once released into the extracellular space during platelet activation, has not been fully elucidated but appears to include thrombus remodelling and receptor cleavage. It has also been hypothesised that platelet lysosomal release may facilitate release of the proinflammatory mediators, IL-1β, tissue factor and **Bcl-3** (Heijnen & van der Sluijs, 2015).

As well as degranulation, activated platelets release extracellular vesicles (EVs) (van der Pol et al., 2012). Their cargo includes not only procoagulant factors but also a broad range of inflammatory modulators, and it is now appreciated that EVs can induce inflammatory changes in endothelium and leukocytes (Vajen et al., 2015). As EVs are able to cross lipid membranes, they can therefore additionally influence the actions of extravascular cell types (Puhm et al., 2021). Clinical studies of inhibitors suggest that $P2Y_{12}$ receptor signalling plays a prominent role in EV release (Gasecka et al., 2020).

4 | CLINICALLY USED PLATELET $P2Y_{12}$ INHIBITORS

Antagonists of platelet $P2Y_{12}$ receptors are widely used in clinical practice for the treatment and secondary prevention of ASCVDs, including coronary artery, cerebrovascular and peripheral artery diseases. **Ticlopidine**, **clopidogrel** and **prasugrel** are orally administered thienopyridine prodrugs whose active metabolites bind selectively and irreversibly to $P2Y_{12}$ receptors (Abbracchio et al., 2019; Hollopeter et al., 2001). Though ticlopidine is generally no longer available, clopidogrel is still extensively prescribed. Clopidogrel has a relatively slow onset time (around 2 h) when compared to newer agents, and offset of significant antiplatelet effect takes around 5 days (Gurbel et al., 2009). Furthermore, a significant proportion

TABLE 1 Effects of key factors contained within platelet alpha granules.

Factor	Effects
β-Thromboglobulin (CXCL7) (Majumdar et al., 1991)	Chemoattraction of neutrophils and fibroblasts, maturation of megakaryocytes, increased tissue plasminogen activator synthesis by fibroblasts
CCL5 (Cognasse et al., 2022)	Interacts with P-selectin to mediate monocyte tissue migration, effector of memory T cells
CD40 ligand (Elgueta et al., 2009)	Binds to CD40 on B cells/dendritic cells, acts as helper T-cell signal, induces germinal centre formation, isotype class switching and antibody production
Defensins Thrombocidins Kinocidins (Leeten et al., 2021)	Antimicrobial activity
Factor V (Harrison & Cramer, 1993)	When activated, forms a component of the prothrombinase complex
Fibrinogen (Blair & Flaumenhaft, 2009)	Facilitates platelet–platelet adhesion, converted to fibrin by thrombin
Fibronectin (Zucker et al., 1979)	Mediates thrombus formation and cell adhesion
Insulin-like growth factor 1 (Hers, 2007)	Stimulates PKB/Akt in a wide range of cell types leading to cell growth and inhibition of apoptosis, as well as potentiating platelet activation
Interleukin-8 (CXCL8) (Chen et al., 2020)	Neutrophil chemotaxis, angiogenesis
P-selectin (CD62P) (Vandendries et al., 2004)	Binds to PSGL-1 to facilitate platelet–leucocyte aggregation and activation
Platelet factor 4 (CXCL4) (Nevzorova et al., 2019)	Neutralises heparin-like molecules, therefore reducing anti-thrombin III activity, contributes to platelet activation, induces platelet death, promotes chemotaxis of leucocytes and fibroblasts
Platelet-derived growth factors (Kardas et al., 2020)	Proliferation of smooth muscle cells, fibroblasts and glial cells
Thrombospondin (Isenberg et al., 2008)	Stimulates platelet aggregation by blocking the antiplatelet effect of nitric oxide, blocks growth factor activity, induces apoptosis of endothelial cells
TNF-α (Pokrovskaya et al., 2020)	Stimulation of inflammatory processes, primarily through the NF-κB and MAPK pathways
TGF-β (Grainger et al., 1995)	Wide range of effects, including on inflammation such as stimulation of resting macrophages, inhibition of B cells and differentiation of T cells
VEGF (Battinelli et al., 2011)	Promotes angiogenesis
Von Willebrand factor (Blair & Flaumenhaft, 2009)	Facilitates platelet–platelet and platelet–endothelium adhesion, stabilises factor VIII

Abbreviations: MAPK, mitogen-activated protein kinase; PKB, protein kinase B; PSGL-1, P-selectin glycoprotein ligand 1.

of the population (approximately one third) are 'resistant' to its effect, partly related to impairment of its enzymatic conversion to the active metabolite by the cytochrome P450, **CYP 2C19** (Matetzky et al., 2004). Prasugrel is a newer thienopyridine with the advantage of reduced variability in levels of platelet inhibition and shorter onset time (30 min) than clopidogrel, but a longer off-set time of around 7 days (Dobesh, 2009). Though still a prodrug, prasugrel's metabolism is not CYP2C19-dependent and does not vary significantly between individuals, there being no evidence of a resistant human phenotype despite some inter-individual variability in response to licensed maintenance doses (Jakubowski et al., 2007).

Reversibly binding, orally administered $P2Y_{12}$ receptor antagonists are also available. **Ticagrelor** is an orally active cyclopentyltriazolopyrimidine with an onset time of around 30 min in stable patients and offset of action between 2 and 5 days (Gurbel et al., 2009). Unlike thienopyridines, ticagrelor is not a prodrug and so is active on $P2Y_{12}$ receptors as soon as it is absorbed. Ticagrelor additionally weakly inhibits **equilibrative nucleoside transporter 1 (ENT1)**, responsible for **adenosine** uptake by erythrocytes and platelets (Armstrong et al., 2014; Aungraheeta et al., 2016).

Cangrelor and selatogrel are reversibly binding, parenterally administered $P2Y_{12}$ receptor antagonists with rapid onset (around 3 and 15 min, respectively), quick offset (recovery of pre-dose levels of platelet inhibition by 60–120 min and 24 h after discontinuation, respectively) and high reliability of effect (Parker et al., 2017; Parker & Storey, 2020). Like ticagrelor, they are not prodrugs. Cangrelor is an ATP analogue that is administered intravenously, and selatogrel is an analogue of 2-phenyl-pyrimidine-4-carboxamide that is administered subcutaneously. The main metabolite of cangrelor weakly inhibits adenosine reuptake, but to a lesser degree than ticagrelor (Armstrong et al., 2014). Neither selatogrel nor its metabolites have any known effects on adenosine kinetics. Selatogrel is not yet licensed nor commercially available but is undergoing a phase III trial of pre-hospital administration in patients with suspected acute myocardial infarction (MI) (NCT04957719).

5 | EFFECTS OF $P2Y_{12}$ RECPTOR ANTAGONISTS ON INFLAMMATION

5.1 | Pharmacodynamic studies

As $P2Y_{12}$ receptors are central to the amplification of platelet activation, inhibition of the receptor in vitro leads to profound reduction in platelet reactivity in response to a range of agonists (Figure 2). This effect is additive to that of **aspirin** whether tested in vitro or in human subjects (Hennigan et al., 2022). In contrast to aspirin, however, $P2Y_{12}$ receptor antagonists and/or their active metabolites have a significant effect in reducing platelet P-selectin expression both in the unstimulated blood samples and when stimulated with agonists such as ADP (Frelinger et al., 2007; Judge et al., 2008; Storey et al., 2002). This leads to a significant reduction in platelet–monocyte and platelet–neutrophil conjugate formation. Increasing the potency and reliability of the antagonism of $P2Y_{12}$ receptors with a newer agent increases the strength of effect on platelet P-selectin expression when compared to clopidogrel (Parker, Gorog, et al., 2020).

Numerous studies have measured circulating or expressed levels of α-granule-derived factors in participants receiving oral $P2Y_{12}$ receptor antagonists. Levels of P-selectin expression or solubilisation and expression of **CD40L** have been demonstrated to be lowered by, for example, loading with clopidogrel in patients with acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI) (Vivekananthan et al., 2004; Xiao & Théroux, 2004). Another study found lower levels of soluble CD40L (sCD40L) and the chemokine **CCL5** (RANTES) in patients with chronic coronary syndrome (CCS) receiving clopidogrel and aspirin when compared to aspirin alone (Heitzer et al., 2006). However, another study failed to demonstrate a significant effect of clopidogrel alone, when compared to aspirin alone, on levels of soluble P-selectin, sCD40L, transforming growth factor-β or MCP-1 in a similar population (Solheim et al., 2006). Patients receiving prasugrel had greater inhibition of CD40L and/or P-selectin expression than when receiving clopidogrel in settings such as CCS and type 2 diabetes (Braun et al., 2008; Parker, Gorog, et al., 2020). When compared to clopidogrel, ticagrelor reduced the release of platelet- and leucocyte-derived EVs, including those expressing P-selectin, during treatment for acute myocardial infarction (Gasecka et al., 2020).

Studies have also measured more general markers of inflammation in patients with coronary syndromes receiving antagonists of $P2Y_{12}$ receptors, in particular CRP. Some studies have shown that clopidogrel reduces CRP, either when assessed at baseline versus on-

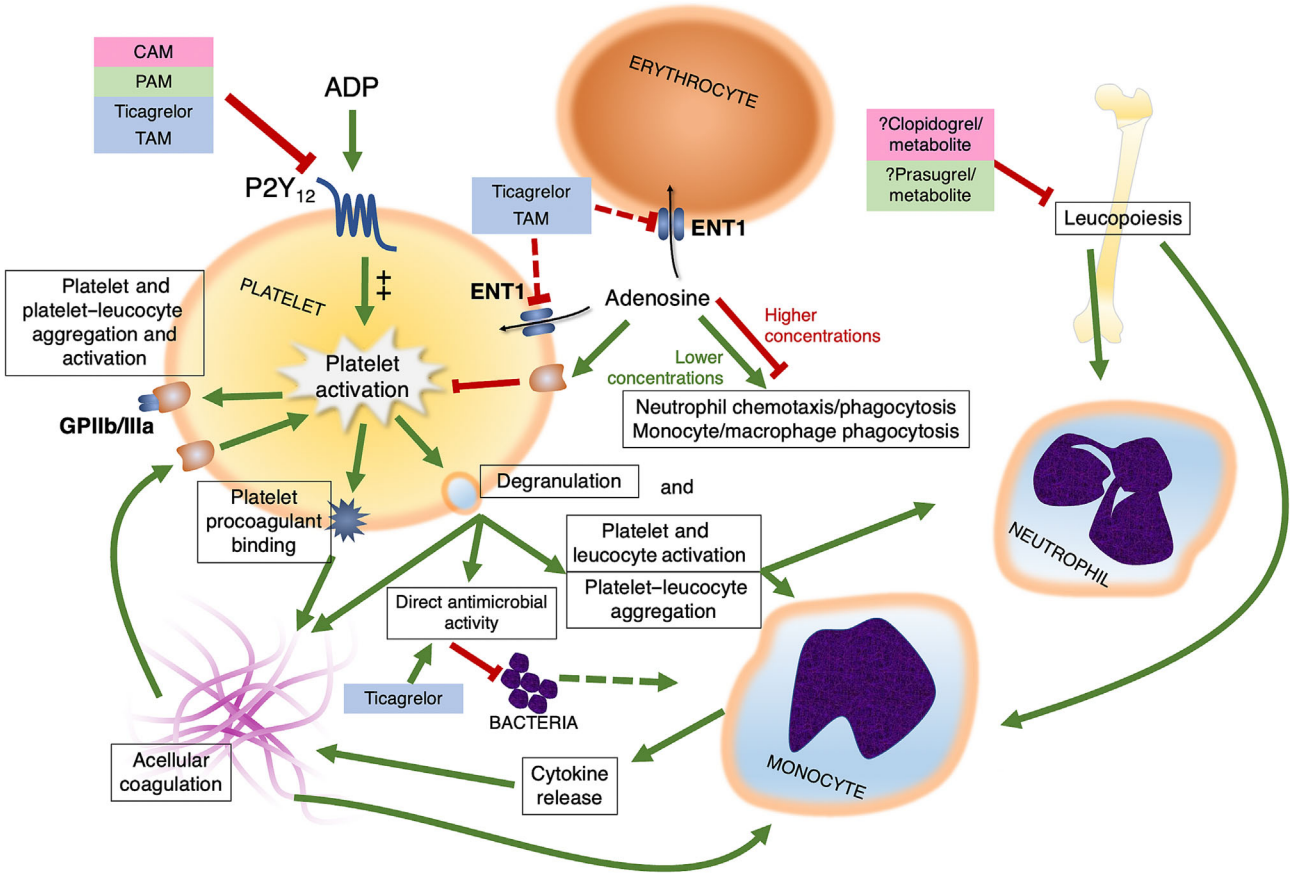

FIGURE 2 On-target and potential off-target effects of commonly used oral platelet $P2Y_{12}$ receptor antagonists on inflammation and related processes. CAM, clopidogrel active metabolite; ENT1, equilibrative nucleoside transporter 1; GPIIb/IIIa, glycoprotein IIb/IIIa; PAM, prasugrel active metabolite; TAM, ticagrelor active metabolite.

treatment or in comparison with aspirin, including those with ACS, CCS and/or undergoing PCI (Chen et al., 2006; Heitzer et al., 2006; Vivekananthan et al., 2004). However, other studies have failed to show a significant effect (Azar et al., 2006; Hajsadeghi et al., 2016; Solheim et al., 2006; Woodward et al., 2004). There is also evidence that TNF-α is significantly reduced by clopidogrel treatment (Chen et al., 2006) and that the effect may be dose-dependent (Gurbel et al., 2006).

In a study of 120 patients undergoing PCI, prasugrel was associated with a greater reduction in high-sensitivity CRP (hs-CRP) compared to clopidogrel, but in another study, levels of hs-CRP were similar between the two drugs, although a lower-than-standard dose of prasugrel was used (Hajsadeghi et al., 2016; Masuyama et al., 2021).

The effect of ticagrelor on CRP has been assessed in comparison to clopidogrel. Studies have shown that in patients with coronary syndromes, ticagrelor treatment is associated with a higher CRP or hs-CRP, accompanied by higher levels of other inflammatory markers such as **IL-6** or endocan, compared to when receiving clopidogrel (Storey et al., 2014; Wei et al., 2017); though another study showed no significant difference, there were trends supporting this effect (Husted et al., 2010). Potential reasons for higher inflammatory markers when receiving ticagrelor than clopidogrel despite more potent antagonism of $P2Y_{12}$ receptors are discussed below.

During primary PCI for myocardial infarction with ST-elevation, in a small study, Abo-Aly et al., (2021) showed that adding cangrelor to aspirin and ticagrelor induced greater inhibition of platelets and reduced circulating levels of proinflammatory factors such as sCD40L and CCL5.

Data concerning effects of $P2Y_{12}$ receptor antagonists on inflammatory markers during other conditions are also available. In a trial of ticagrelor in patients with pneumonia, when compared to placebo, ticagrelor inhibited platelet–leucocyte aggregation and was associated with a significant reduction in circulating IL-6 levels and a shorter requirement for supplemental oxygen (Sexton et al., 2018). There were no significant effects on other inflammatory markers, though, in contrast to IL-6, these were not elevated above the reference range.

5.2 | Effects during in vivo experimental inflammation

Important data on the effects of $P2Y_{12}$ receptor antagonists on acute inflammation have also been obtained using in vivo experimental models. These allow controlled and comprehensive study of the inflammatory response. In particular, the use of experimental endotoxaemia has greatly informed our understanding of the interaction between platelet $P2Y_{12}$ receptors and inflammation (Suffredini & Noveck, 2014). Endotoxin stimulates monocyte activation via **TLR4**. As well as the obvious relevance to gram-negative sepsis, TLR4 acts as a damage-associated molecular pattern receptor, and so this pathway is applicable to other forms of tissue damage, including atherogenesis and atherothrombosis.

In mouse or rat models of endotoxaemia, antagonism of $P2Y_{12}$ receptors with clopidogrel reduced detectable levels of the proinflammatory cytokines IL-6 and TNF-α, associated with less severe liver and lung injury (Hagiwara et al., 2011; Winning et al., 2009), though this effect was not seen in a pig model (Lipcsey et al., 2005). In another study, prasugrel significantly inhibited the release of proinflammatory cytokines during murine endotoxaemia (Totani et al., 2012).

Experimental human endotoxaemia has also been used to study the effects of antagonists of $P2Y_{12}$ receptors on acute inflammation, summarised in Table 2. Taken together, these suggest that antagonism of platelet $P2Y_{12}$ receptors leads to reduced acute inflammatory response when stimulated via TLR4 but that the ability of $P2Y_{12}$ receptor antagonists to reduce acute inflammation may be affected by concurrent treatment with aspirin, as is common in many patients with ASCVD. This is being studied further in the WILLOW TREE trial (NCT03869268), expected to report its results this year.

The murine caecal ligation and puncture (CLP) model of intrabdominal polymicrobial sepsis has likewise been used to study the role of $P2Y_{12}$ receptors in inflammation. Clopidogrel in wild-type (WT) mice mimicked the effect of $P2Y_{12}$ knockout (KO) in preventing CLP-induced increases in P-selectin expression and platelet–leucocyte aggregation, which was associated with protection from acute lung and liver injury (Liverani et al., 2016). Levels of TNF-α and IL-6 after CLP were significantly lower in $P2Y_{12}$-KO, than in WT mice. Notably, however, clopidogrel significantly reduced leucocyte counts after CLP in both WT and KO mice, suggesting a $P2Y_{12}$-independent mechanism. On the other hand, another study of the murine CLP model failed to show benefits of clopidogrel treatment or deletion of platelet-specific $P2Y_{12}$ receptors (Rabouel et al., 2021). Potential explanations for the discrepancy in findings between the two groups include that the models were not necessarily equivalent given some differences in circulating cell count responses to sepsis. The effect of clopidogrel has also been studied in murine models of chest sepsis caused by *Streptococcus pneumoniae* or *Klebsiella pneumoniae*, with no significant influence seen on host response to infection (Claushuis et al., 2019; van den Boogaard et al., 2015).

Murine CLP has also been used to study the effects of ticagrelor (Rahman et al., 2013). During polymicrobial sepsis, ticagrelor significantly inhibited the formation of platelet–neutrophil aggregates and acute lung injury, when assessed by histological scoring, bronchoalveolar fluid neutrophil count or weight of lung oedema. Ticagrelor had no significant effect on neutrophil CD11b expression or formation of lung chemokines.

Experimental models of infective endocarditis have similarly been utilised. In a rat model of *Enterococcus faecalis* or *Streptococcus gallolyticus* infective endocarditis, neither aspirin nor ticlopidine when given alone influenced vegetation weight, but combining the two drugs significantly reduced the chance of developing endocarditis and infective burden when it did develop (Veloso et al., 2015). A similar finding was made in a rabbit model (Nicolau et al., 1999). Whether the observed effect is due to effects on thrombosis, inflammation, infection or a combination of these remains unclear. It has been hypothesised that in *Staphylococcus aureus* bacteraemia, for example, potent antagonism of $P2Y_{12}$ receptors may prevent infection-induced platelet death and

TABLE 2 Studies of $P2Y_{12}$ receptor antagonists during human experimental endotoxaemia.

Paper	Sample population	Endotoxin regimen	Treatment allocation	Key findings
Spiel et al. (2012)	20 healthy males	2-ng·kg^{-1} IV bolus	60-mg loading dose of prasugrel or placebo 2 h before endotoxin in a crossover design	Prasugrel inhibited platelet activation responses during endotoxaemia. Release of vWF during endotoxaemia appeared to antagonise the ability of prasugrel to inhibit platelet plug formation in high shear stress conditions
Thomas et al. (2015)	30 healthy males	2-ng·kg^{-1} IV bolus	No drug (n = 10), clopidogrel 75 mg OD (n = 10) or ticagrelor 90 mg BD (n = 10) for 1 week before endotoxin in a parallel-group design	During endotoxaemia, both clopidogrel and ticagrelor significantly reduced peak levels of TNF-α and IL-6. Ticagrelor additionally significantly inhibited CCL2 (MCP-1) and G-CSF and increased peak levels of IL-8. Both drugs reduced platelet P-selectin expression, PMA and PNA formation. Reduced levels of inflammation when receiving a $P2Y_{12}$ receptor antagonist were associated with less prothrombotic change in fibrin clot dynamics
Kiers et al. (2017)	40 healthy males	1-ng·kg^{-1} IV bolus, then 1-ng·kg^{-1} IV infusion over 1 h	Ticagrelor (180-mg loading dose then 90 mg BD) plus aspirin (160-mg loading dose then 80 mg OD) (n = 10); clopidogrel (300-mg loading dose then 75 mg OD) plus aspirin (n = 10); aspirin alone (n = 10) or placebo (n = 10) for 7 days prior to endotoxin in a parallel-group design	Neither ticagrelor nor clopidogrel (both given alongside aspirin) significantly affected cytokine release during endotoxaemia. Aspirin, when given alone, increased release of TNF-α when compared to no drug or aspirin plus ticagrelor. Mechanistic studies suggested that the proinflammatory effect of aspirin was due to inhibition of platelet PGE_2 release

Abbreviations: BD, twice daily; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; OD, once daily; PMA, platelet–monocyte aggregate; PNA, platelet–neutrophil aggregate; vWF, von Willebrand factor.

therefore preserve the antimicrobial actions of platelets provided by release of factors such as defensins (Leeten et al., 2021), though given that this is α-degranulation mediated, it is not clear what would be the optimal balance of inhibition and permittance of α-degranulation.

Myocardial infarction is also an inflammatory stimulus, and the effects of $P2Y_{12}$ inhibitors on inflammatory processes in animal models of myocardial infarction have been studied. In a murine model of myocardial infarction, antagonism of $P2Y_{12}$ receptors with prasugrel reduced proinflammatory emergency haematopoiesis, but this appeared to be mediated by a non-platelet mechanism (Seung et al., 2022). $P2Y_{12}$ KO also reduced myocardial platelet and neutrophil accumulation during reperfusion after experimental myocardial infarction (von Elverfeldt et al., 2014), a similar effect being seen when receiving the $P2Y_{12}$ receptor antagonist prasugrel, in a murine model of autoimmune myocarditis (Schmidt et al., 2021). Neutrophil CD11b was reduced by ticagrelor in a murine model of myocardial infarction and reperfusion (Mauler et al., 2019). Though not yet entirely clear and excluding non-platelet-dependent mechanisms, the effects of $P2Y_{12}$ receptor antagonists in these settings are probably a combination of anti-inflammatory action limiting tissue damage and antithrombotic actions reducing microthrombosis with resulting reductions in ongoing ischaemia or progressive infarction. Effects of ticagrelor on ischaemia–reperfusion injury have been linked to its pleiotropic effect on adenosine reuptake, which is discussed later.

5.3 | Insights from studies of clinical outcomes

It is well established from large randomised clinical trials that adding an oral antagonist of $P2Y_{12}$ receptors to aspirin treatment reduces the risk of MACE in ACS and high-risk CCS (Parker & Storey, 2016a). Similarly, $P2Y_{12}$ receptor antagonists are used to reduce MACE in cerebrovascular and peripheral artery disease (Parker, Schulte, et al., 2020). It seems clear therefore that $P2Y_{12}$ receptor antagonists can reduce the frequency and/or the effects of atherothrombosis. Atherothrombosis is a thrombo-inflammatory phenomenon, and though most focus has been given to effects on the thrombotic component, it is plausible that anti-inflammatory effects also contribute.

Large randomised controlled trials (RCTs) of clopidogrel and placebo or prasugrel and clopidogrel in ACS showed no significant difference in all-cause or non-cardiovascular mortality between treatments (Chen et al., 2005; CURE Trial Investigators, 2001; Wiviott et al., 2007). However, in the PLATelet inhibition and patient Outcomes (PLATO) trial, which studied ticagrelor and clopidogrel in patients with ACS, all-cause mortality was significantly lower in the group receiving ticagrelor, with numerically lower non-cardiovascular death (Wallentin et al., 2009). This was contributed to by significantly fewer fatal pulmonary infections, and there was also a reduction in the number of non-fatal infections (Storey et al., 2014).

Observational studies have suggested that treatment with clopidogrel may increase the risk of developing community-acquired pneumonia but conversely may reduce the severity of conditions such as pneumonia or *S. aureus* bacteraemia when these do occur (Caffrey et al., 2022; Gross et al., 2013; Winning et al., 2009, 2010). Another study in patients with sepsis requiring intensive care unit admission suggested that there may be a benefit of clopidogrel when given alone but not in combination with aspirin (Otto et al., 2013). Observational data have also shown a significantly reduced risk of gram-positive infections in ACS patients receiving ticagrelor compared to clopidogrel (Lupu et al., 2020).

Few RCTs have studied the effect of $P2Y_{12}$ receptor antagonists on inflammation in non-cardiovascular conditions but nevertheless have demonstrated some potentially promising findings. The Prasugrel IN Asthma (PRINA) trial randomised 26 patients with chronic asthma to receive prasugrel or placebo in a crossover study. Using mannitol challenge to assess bronchial responsiveness, prasugrel significantly reduced bronchial hyperreactivity, though it had no influence on exhaled levels of **NO** (Lussana et al., 2015). More recently, an RCT of ticagrelor or placebo in 60 patients with pneumonia found that, compared to placebo, ticagrelor reduced levels of IL-6 and platelet–leucocyte aggregates (Sexton et al., 2018). Promisingly, there was also some evidence of modest beneficial effects on lung function.

Most recently, $P2Y_{12}$ receptor antagonists have been trialled in the setting of COVID-19. COVID-19 infection can lead to an intense thrombo-inflammatory response, and detectable markers of platelet activation, including those of α-degranulation, can be profoundly raised (Gąsecka et al., 2021; Gorog et al., 2022; Parker & Storey, 2021b). Despite this, trials of $P2Y_{12}$ receptor antagonists in critically or non-critically ill hospitalised patients with COVID-19 have been disappointing, showing no significant improvements in outcomes such as the requirement for organ support (Berger et al., 2022; Bradbury et al., 2022).

5.4 | Limitations in the interpretation of evidence from clinical studies

Several factors may complicate the interpretation of data from observational or interventional clinical studies when considering how these demonstrate the role of the platelet $P2Y_{12}$ receptors in inflammation.

In studies of $P2Y_{12}$ receptor antagonists in settings such as ACS or PCI, it may be difficult to disentangle direct effects on inflammation from indirect effects on the burden of proinflammatory infarction, which is known to be less with increasing potency of $P2Y_{12}$ receptor antagonism (Khan et al., 2016), though peri-procedural myocardial infarction was not reduced by increasing potency, after PCI for CCS (Orme et al., 2018). Conceivably, even studies in conditions such as pneumonia may be affected by differential effects on type 1 and type 2 myocardial infarctions that often accompany severe infection, though study in this area is very much lacking (DeFilippis et al., 2019).

Observational studies may be particularly difficult to interpret given that patients receiving or not receiving $P2Y_{12}$ receptor antagonists as part of their usual clinical care will inherently have differing risk profiles, which, despite statistical techniques, are challenging to completely adjust for. Similarly, the choice of $P2Y_{12}$ receptor antagonist is likely be influenced by clinical characteristics. This underlines the importance of obtaining robust data from RCTs.

As well as platelet $P2Y_{12}$ receptors, non-platelet $P2Y_{12}$ receptors may also play a role in inflammation that may contribute to the effects seen in studies of $P2Y_{12}$ receptor antagonists. Dendritic cell $P2Y_{12}$ receptors plays a role in endocytosis and **IL-12** production that may affect T-cell responses (Schnurr et al., 2005). $P2Y_{12}$ receptors on vascular smooth muscle cells are involved in expression of proinflammatory factors regulating monocyte chemotaxis and have a role in inflammatory processes such as early atherogenesis and allograft vasculopathy (Harada et al., 2011; Satonaka et al., 2015; West et al., 2014). Likewise, monocyte $P2Y_{12}$ receptors may play a role in modulation of function (Micklewright et al., 2018). $P2Y_{12}$ receptors of undetermined location also mediates **leukotriene E_4**-induced pulmonary inflammation (Paruchuri et al., 2009).

Furthermore, as well as antagonism of $P2Y_{12}$ receptors, pleiotropic effects of drugs may play a role in determining the effects on inflammation and infection seen during clinical studies. The thienopyridines have long been associated with cytopaenias, in particular leucopaenia. In the case of ticlopidine, this may occur to a clinically significant extent in around 5% of patients during prolonged administration and has led to its near abandonment (Janzon, 1996). Though clinically meaningful leucopaenia occurs much less commonly with clopidogrel, there is evidence from animal and human studies that clopidogrel still significantly reduces leucocyte count (Liverani et al., 2016; Nelson et al., 2022; Storey et al., 2014). Effects of prasugrel and other $P2Y_{12}$ receptor antagonists on leucocyte count have not been well studied, though in vitro studies have suggested that prasugrel metabolites may inhibit neutrophil function via a non-$P2Y_{12}$ receptor-mediated pathway (Liverani et al., 2012).

There is no evidence that ticagrelor reduces leucocyte count during maintenance therapy (Storey et al., 2014), but its additional property of weak inhibition of ENT1 may also contribute to observed effects on inflammation. Though early evidence suggested that ticagrelor significantly increased plasma levels of adenosine, multiple subsequent clinical studies attempting to demonstrate this effect during therapeutic administration have shown no significant difference, compared to clopidogrel, no drug or during offset of ticagrelor's

antiplatelet effect (Bonello et al., 2014; Kiers et al., 2017; Orme et al., 2018; Ow et al., 2020). Therefore, although in vitro studies demonstrate that ticagrelor certainly inhibits adenosine reuptake by erythrocytes and platelets (Nylander et al., 2013; Parker & Storey, 2016b), the clinical significance of this effect at therapeutic plasma concentrations of ticagrelor is not completely clear. As well as augmenting the antiplatelet effect of $P2Y_{12}$ receptor antagonists (Nylander et al., 2013), adenosine has dimorphic effects on neutrophil and monocyte function, which are potentiated by ticagrelor in vitro (Alsharif et al., 2015). At lower concentrations, adenosine primarily stimulates high-affinity **A_1** receptors, with downstream effects that are more proinflammatory than anti-inflammatory, including promotion of neutrophil chemotaxis and phagocytosis and macrophage phagocytosis (Barletta et al., 2012). At higher concentrations, adenosine primarily acts on low-affinity **A_{2A}** and **A_{2B}** receptors, with downstream effects that are more anti-inflammatory than proinflammatory, including down-regulation of cytokine release (Haskó & Pacher, 2012). Ticagrelor-related increase in adenosine exposure has also been associated with other effects relevant to inflammation such as up-regulation of **cyclooxygenase 2** and **nitric oxide synthase** in animal models (Nanhwan et al., 2014; Ye et al., 2015). Finally, there is some evidence that ticagrelor, but not thienopyridines, may have direct antimicrobial properties, including against organisms that are antibiotic-resistant (Lancellotti et al., 2019). This appears to be an effect particularly against gram-positive organisms. For example, in a murine model of *S. aureus* infective endocarditis, treatment with ticagrelor, but not clopidogrel, reduced vegetation formation compared to drug-free controls, which appeared to be related to effects on bacterial toxin production and endothelial adherence (Oury et al., 2023).

6 | FUTURE WORK AND SCOPE FOR CLINICAL UTILITY OF $P2Y_{12}$ RECEPTOR ANTAGONISTS IN INFLAMMATION

Given that antagonists of $P2Y_{12}$ receptors are already utilised for the treatment and prevention of ASCVD, the potential for optimising and expanding their use in this population is seemingly most feasible. For example, current evidence suggests that prolonged antagonism of $P2Y_{12}$ receptors in patients with high-risk CCS can offer net benefits in clinical outcomes (Parker & Storey, 2021a), though determining whether any anti-inflammatory and antithrombotic effects are contributory is difficult to assess. Whether $P2Y_{12}$ receptor antagonists find a significant role in non-ASCVD inflammatory conditions in addition to or instead of existing drug treatments remains to be seen. This will primarily depend on whether clinical benefits that outweigh any risks can be robustly demonstrated in appropriately powered RCTs. So far, the most powered RCTs to study hard clinical outcomes in patients receiving $P2Y_{12}$ receptor antagonists for a non-cardiovascular condition have been in the setting of COVID-19. Although trials have demonstrated that, in severe COVID-19, other forms of anti-inflammatory therapy such as corticosteroids and monoclonal antibodies against the IL-6 receptor may significantly improve clinical outcomes (Zeraatkar et al., 2022), those of $P2Y_{12}$ receptor antagonists have been disappointing, as we have discussed. Nevertheless, both animal and human studies have some conflicting results that may point to the benefit of $P2Y_{12}$ receptor antagonism in inflammatory conditions being situation-dependent. Notably, in the setting of ASCVD, not all anti-inflammatory therapies appear to be equally efficacious; for example, **colchicine** and **canakinumab** reduced cardiovascular risk, but **methotrexate** had no significant effect (Ridker et al., 2017, 2019; Tardif et al., 2019). In the area of sepsis, there is still debate as to whether anti-inflammatory therapies, in general, can be beneficial due to the careful balance of preserving the physiological mechanisms of fighting infection whilst avoiding inappropriate overstimulation of inflammation (Nedeva et al., 2019), and clinical trials of any anti-inflammatory therapies in sepsis have overall been disappointing. Whether additional properties beyond antithrombotic and anti-inflammatory effects are relevant remains to be explored: Ticagrelor's apparent direct antimicrobial properties are certainly intriguing, but if and how they complement existing antibiotic pharmacotherapy is not yet clear. However, these properties may also hypothetically mitigate any loss of defence against infection caused by the anti-inflammatory effect of $P2Y_{12}$ receptor antagonism.

There are numerous other non-cardiovascular conditions in which the anti-inflammatory properties of $P2Y_{12}$ receptor antagonists may be hypothetically able to play a useful role, for example, chronic inflammatory diseases such as rheumatoid arthritis (RA). There is some limited evidence that treatment with ticagrelor may be of benefit in patients with methotrexate-resistant RA (Garshick et al., 2021), though it remains unclear if the effect seen was mediated via antagonism of $P2Y_{12}$ receptors or by potentiating effects of methotrexate on adenosine accumulation, and the effects of $P2Y_{12}$ receptor antagonists in animal models of RA are conflicting (Entsie et al., 2023). Though a range of other existing anti-inflammatory therapies exist for these conditions, a chronic inflammatory state is strongly linked to cardiovascular risk (Hansildaar et al., 2021), and it is plausible, but not yet determined, that the additional anti-inflammatory and antithrombotic effects may contribute to potential long-term net benefits.

The main drawback of $P2Y_{12}$ receptor antagonists as anti-inflammatory agents, similar to their use as antithrombotic drugs, is likely to be an increase in bleeding risk, though the magnitude of this risk when used outside of combination antithrombotic therapy appears to be similar to that of aspirin (CAPRIE Steering Committee, 1996; Johnston et al., 2016) and has to be weighed against potential benefits from the antithrombotic and anti-inflammatory effects to determine net clinical benefit in the particular population. The availability of rapid reversal strategies for $P2Y_{12}$ receptor antagonists may help to address some concerns. For example, bentracimab, a novel monoclonal antibody fragment against ticagrelor and its active metabolite, may be one such strategy (Bhatt et al., 2019).

Mechanistically, the effect of inflammation, mediated by platelet $P2Y_{12}$ receptors, on leucocytes has focussed on monocytes and neutrophils, and more work is needed to determine if other cell types play

a role. Mast cells, for example, can both activate and be activated by platelets (Boyce, 2007; Karhausen et al., 2020), though it has not been well determined if $P2Y_{12}$ receptors are involved in mediating these effects. Platelets also play a role in adaptive and innate immunity (Marcoux et al., 2021). Platelets can process and present antigens to $CD8^+$ T cells via proteasomal activity, primarily medicated by major histocompatibility complex 1, which is contained within alpha granules (Zufferey et al., 2014). Factors such as CD40L also stimulate T- and B-cell function (Blumberg et al., 2009). Furthermore, platelets respond to antibodies, expressing a range of Fc receptors. Most notably, this includes the **Fc receptor for immunoglobulin G IIA (FcγRIIA)**, which binds immune complexes and microorganisms and is known to play a role in a wide range of inflammatory, autoimmune and infective conditions (Marcoux et al., 2021). That $P2Y_{12}$ receptors are directly involved in the function and regulation of these processes is not fully established, but, given that aspects of platelet activation such as degranulation and EV release appear important, its signalling would be predicted to enhance them. As discussed earlier, the further exploration of the role of non-platelet $P2Y_{12}$ receptors in inflammation is additionally needed.

7 | CONCLUSIONS

The $P2Y_{12}$ receptor and its associated downstream pathways play a central role in the amplification of platelet activation, potentiating effects such as platelet aggregation, degranulation, shape change and platelet procoagulant activity. Degranulation in particular mediates proinflammatory effects, including the formation of platelet–leucocyte aggregates via platelet P-selectin binding to leucocyte PSGL-1. Studies of $P2Y_{12}$ receptor antagonists have shown strong inhibitory effects on degranulation and platelet–leucocyte aggregation. Interpreting data from clinical studies of $P2Y_{12}$ receptor antagonists is complicated by pleiotropic effects of thienopyridines and ticagrelor, but overall, these support a proinflammatory role of platelet $P2Y_{12}$ receptors and suggest that inhibition of the receptor, alongside effects on thrombus formation, is potentially useful in a range of inflammatory conditions from atherosclerosis to sepsis and beyond.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos et al., 2021; Alexander, Fabbro et al., 2021a, b; Alexander, Kelly et al., 2021a, b).

AUTHOR CONTRIBUTIONS

William A. E. Parker: Writing—original draft (lead); writing—review and editing (equal). **Robert F. Storey:** Conceptualization (lead); writing—review and editing (equal).

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DATA AVAILABILITY STATEMENT

No original data are associated with this manuscript.

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